Drug Monograph

A - Drug Name

polatuzumab vedotin

COMMON TRADE NAME(S): Polivy™

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B - Mechanism of Action and Pharmacokinetics

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate which consists of a humanized IgG1 monoclonal antibody and an anti-mitotic agent, monomethyl auristatin E (MMAE) covalently attached by a cleavable linker. Upon binding to CD79b on the surface of B cells, polatuzumab vedotin is endocytosed. Once inside the cell, lysosomal proteases cleave the linker enabling intracellular delivery of MMAE. The released MMAE binds to microtubules and kills dividing cells by inhibiting cell division (G2/M phase) and inducing apoptosis.

Absorption	Peak plasma levels	Unconjugated MMAE: ~2.5 days (after first dose)
Distribution	PPB	MMAE: 71% - 77%
Metabolism	Polatuzumab vedotin undergoes catabolism to produce small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE related catabolites.	
Elimination	Half-life	Antibody-conjugated MMAE: ~ 12 days (at cycle 6) Unconjugated MMAE: ~ 4 days (after first dose)
	Feces	Majority of MMAE excreted in feces

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C - Indications and Status

Health Canada Approvals:

- Diffuse large B-cell lymphoma (DLBCL)

(Includes conditional approvals)

Refer to the product monograph for a full list and details of approved indications

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D - Adverse Effects

Emetogenic Potential: Low

The following table lists adverse effects that occurred in ≥5% of relapsed or refractory DLBCL patients treated with polatuzumab vedotin in combination with bendamustine and rituximab compared with bendamustine and rituximab alone. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypotension (9%)	E
	Tachycardia (9%)	E
Dermatological	Rash, pruritus (13%)	E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia, weight loss (27%)	E
	Constipation (18%)	E
	Diarrhea (38%)	E
	Gastroesophageal reflux disease (7%)	E
	Nausea, vomiting (33%) (2% severe)	E
General	Fatigue (40%)	E
Hematological	Myelosuppression ± infection (47%) (including anemia) (40%	E

	severe)	
Hepatobiliary	Hepatotoxicity (4%) (severe)	E
	↑ LFTs (9%)	E
	↑ Lipase (7%)	E
Hypersensitivity	Infusion related reaction (33%) (may be severe)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (16%) (↓ K, ↓ albumin, ↓ Ca, ↓ PO4)	E
	Tumor lysis syndrome (8%)	E
Musculoskeletal	Musculoskeletal pain (7%)	E
Nervous System	Anxiety (7%)	E
	Dizziness (13%)	E
	Dysgeusia (7%)	E
	Headache (9%)	E
	Insomnia (9%)	E
	Leukoencephalopathy - Progressive multifocal leukoencephalopathy (PML) (rare)	E
	Peripheral neuropathy (20%) (0% severe)	E
Respiratory	Cough, dyspnea (16%)	E
	Pneumonitis (4%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for polatuzumab vedotin include myelosuppression ± infection, fatigue, diarrhea, infusion related reactions, nausea, vomiting, anorexia, weight loss, peripheral neuropathy, constipation, abnormal electrolyte(s), and rash/pruritus.

Infusion-related reactions, including severe cases have been reported. Symptoms include fever, chills, flushing, dyspnea, hypotension, and urticaria and may be delayed, occurring as late as 24 hours after administration.

Tumor lysis syndrome (TLS) may occur; risk of TLS is higher in patients with a high tumor burden and/or with rapid tumor proliferation.

Hepatotoxicity may be increased in patients with preexisting liver disease, elevated baseline liver enzymes, and/or concomitant hepatotoxic medication. Most events were low grade and reversible.

Serious, life-threatening, or fatal **infections**, including opportunistic infections such as pneumonia

(including Pneumocystis jirovecii and other fungal pneumonia), bacteremia, sepsis, herpes zoster infection, and cytomegalovirus infection have been reported. Cases of progressive **multifocal leukoencephalopathy** (PML) have been observed.

Peripheral neuropathy has been reported and can occur as early as the first cycle of treatment with increasing risk after sequential doses, but no grade 3-5 events were reported. Patients with pre-existing peripheral neuropathy may experience worsening of their condition. Peripheral neuropathy is primarily sensory; however, motor and sensorimotor peripheral neuropathy may also occur. The median time to onset was 1.8 months. Neuropathy completely resolved in 61% of patients.

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E - Dosing

Refer to protocol by which patient is being treated.

Premedication (Prophylaxis for Infusion Reactions):

- If not already pre-medicated, administer an antihistamine and anti-pyretic at least 30 to 60 minutes prior to polatuzumab vedotin administration.

Other Supportive Care:

- Administer tumor lysis syndrome prophylaxis for patients at increased risk of tumor lysis syndrome.
- Consider anti-infective prophylaxis. (e.g., PJP, herpes virus)
- Consider prophylactic G-CSF administration for neutropenia.

Adults:

Intravenous: 1.8 mg/kg Every 21 days for 6 cycles

- Administer in combination with bendamustine and rituximab (for relapsed/refractory DLBCL). Refer to BEND+POLA+RITU for bendamustine and rituximab dosing.

Dosage with Toxicity:

Dose levels - Relapsed/Refractory DLBCL:

Dose level	Polatuzumab vedotin Dose (mg/kg)*
0	1.8
-1	1.4
-2	Discontinue

*Do not re-escalate once dose is decreased

Dose Modifications - Relapsed/Refractory DLBCL:

Toxicity on Day 1 of any cycle	Grade	Polatuzumab vedotin Dose
Peripheral neuropathy	Grade 2 and 3	Hold* If recovery in ≤14 days: • Resume (with the next cycle) at 1 dose level ↓ • If recurs, discontinue If recovery in >14 days: • Discontinue
	Grade 4	Discontinue
Neutropenia	≥ Grade 3	Hold* Consider G-CSF for subsequent cycles. If recovery occurs in ≤7 days: • Resume at same dose level If recovery in >7 days: • Resume at same dose level. Refer to the POLA+BEND+RITU regimen monograph for dose modifications of bendamustine and rituximab.

Thrombocytopenia	≥ Grade 3	Hold* If recovery occurs in ≤7 days: • Resume at same dose level If recovery in >7 days: • Resume at same dose level. Refer to the POLA+BEND+RITU regimen monograph for dose modifications of bendamustine and rituximab.
Progressive multifocal leukoencephalopathy (PML)	Any	Hold and investigate; discontinue if confirmed.
Serious infections	Any	Discontinue

*Do not retreat until ANC > 1 x 10^9/L, platelets > 75 x 10^9/L and peripheral neuropathy ≤ grade 1.

Management of Infusion-related Reactions:

Also refer to the CCO guideline for information on Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge

1-3	• Stop the infusion.
	• Manage the symptoms.
	
	Restart:
	
	• Once symptoms have resolved, restart (if applicable) at 50% of the rate achieved prior to interruption.
	• If no reaction occurs, escalate the rate at no more than 50 mg/hour every 30 minutes.
	• Discontinue for:
	  ◦ Grade 3 wheezing, bronchospasm, or generalized urticarial
	  ◦ Recurrent grade 2 wheezing or urticaria, or recurrence of any grade 3 symptoms
		• Infuse polatuzumab vedotin over 90 minutes; if no infusion-related reaction occurs, infuse subsequent infusions over 30 minutes.
		• Administer pre-medication for all cycles.

4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue (do not re-challenge).

Dosage with Hepatic Impairment:

Hepatic Impairment	Polatuzumab vedotin Dose (mg/kg)
Total bilirubin ≤1.5 x ULN or AST/ALT ≤2.5 x ULN	No dose adjustment required
Total bilirubin >1.5 x ULN or AST/ALT >2.5 x ULN	Avoid use. MMAE exposure may be increased and may lead to an increased incidence of adverse events.

Dosage with Renal Impairment:

Renal Impairment	Polatuzumab vedotin Dose (mg/kg)
Mild or moderate (CrCl ≥30 mL/min)	No dose adjustment required
Severe (CrCl <30 mL/min) or ESRD	Has not been studied

Dosage in the elderly:

No dose adjustment required. Patients ≥ 65 of age had a higher incidence of ≥grade 3 adverse events and treatment discontinuation compared with younger patients.

Children:

Safety and efficacy in children have not been established.

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F - Administration Guidelines

- **DO NOT** administer as an IV push or bolus.
- Reconstitute using sterile water for injection, immediately before dilution.
- Dilute in 0.9% sodium chloride, 0.45% sodium chloride or 5% dextrose IV infusion bag with a minimum volume of 50mL. Final concentration must be 0.72-2.7 mg/mL.
- Do not shake vial or IV bag. Agitation can result in aggregation.
- Infuse via dedicated line equipped with a sterile, non-pyrogenic, low-protein binding in-line or addon filter (0.2 or 0.22 µm size) and catheter.
- Administration of Polatuzumab vedotin, bendamustine, and rituximab can occur any order on Day 1 of each cycle.
- Initial dose should be administered over 90 minutes. If well tolerated, the subsequent doses may be administered over 30 minutes.
- Patients should be monitored for infusion-related reactions during and for at least 90 minutes following the first infusion, and for at least 30 minutes following subsequent infusions.
- If a polatuzumab vedotin dose is missed, administer as soon as possible. Adjust cycle schedule in order to maintain a 21-day interval between doses.
- No incompatibilities have been observed between polatuzumab vedotin and:
    - IV infusion bags with polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP).
    - Infusion sets or infusion aids with PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polyetherurethane (PEU), or fluorinated ethylene propylene (FEP), or polytetrafluorethylene (PTFE).
    - Filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).
- Store unopened vials at 2-8°C in the original carton to protect from light.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any components of the formulation.

Other Warnings/Precautions:

- Patients with ≥ grade 2 peripheral neuropathy or prior allogeneic hematopoietic stem cell transplantation (HSCT) were excluded from clinical trials.
- Ingestion of grapefruit, starfruit, Seville oranges, their juices or products while on polatuzumab therapy may increase MMAE plasma concentrations as these products have CYP3A4 inhibitory activity. Monitor closely for signs of toxicity.
- Caution with driving or using machinery as peripheral neuropathy, fatigue, and dizziness may occur with treatment.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Documented in animals
- Teratogenicity: Documented in animals
- Mutagenicity: No
- Embryotoxicity: Documented in animals
  Polatuzumab is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **9 months** after the last dose in females and for at least **6 months** after the last dose in males.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **3 months** after the last dose.
- Fertility effects: Documented in animals
  Fertility may be impaired in males.

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H - Interactions

MMAE is a P-gp and CYP3A4/5 substrate and is a weak time-dependent inhibitor of CYP3A4/5. It does not competitively inhibit CYP3A4/5 or P-gp at clinically relevant concentrations.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ polatuzumab vedotin exposure. (↑ AUC of unconjugated MMAE by 48%)	↓ metabolism of polatuzumab vedotin	Monitor for signs of toxicities
Strong CYP3A4 inducers (i.e. phenytoin, rifampin, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ polatuzumab vedotin concentration and/or efficacy.	↑ metabolism of polatuzumab vedotin	Monitor for efficacy

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle; consider more frequently for patients with Grade 3 or 4 neutropenia or thrombocytopenia
Liver function tests	Baseline, before each cycle and as clinically indicated
Renal function tests	Baseline, before each cycle and as clinically indicated
Electrolytes, including sodium, potassium, magnesium and uric acid	Baseline and as clinically indicated
Clinical toxicity assessment for infusion-related reactions, neuropathy, TLS, PML, bleeding, infection	As clinically indicated

(including opportunistic), fatigue, and cardiovascular, nervous system, GI, or skin effects	

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Polatuzumab Vedotin with Bendamustine and Rituximab (Biosimilar) - Relapsed or Refractory Diffuse Large B-cell Lymphoma

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K - References

BC Cancer Protocol Summary for Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Not Eligible for Transplant using Polatuzumab Vedotin, Bendamustine and rituximab; April 2022.

Liebers N, Duell J, Fitzgerald D, et al. Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas. Blood Advances 2021;5(13):2707-2716

Product Monograph: Polivy (polatuzumab vedotin). Hoffman-La Roche Limited. Mississauga, Ontario. April 2021.

Prescribing Information: Polivy (polatuzumab vedotin). Genentech, Inc. South San Francisco, CA. September 2020.

Sehn L, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2019; 37. https://doi.org/10.1200/JCO.19.00172.

December 2022 Added indication in Dosing and Dose modifications sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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